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# Acetaminophen

CAS #103-90-2

Swiss CD-1 mice, at 0.0, 0.25, 0.5, 1.0% in feed

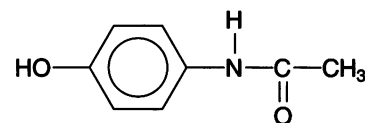
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NTIS #PB85204667/AS

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Acetaminophen (ACET), a common over-the-counter analgesic agent, was tested for its effects on reproduction and fertility in CD-1 mice, following the RACB protocol (Reel et al., *Fundam Appl Toxicol* 18: 233-239 [1992]). Data on body weights, clinical signs, and food and water consumption from a 2-week dose-range-finding study (Task 1) were used to set exposure levels for the Task 2 continuous cohabitation phase at 0.25, 0.5, and 1.0% in the diet. Feed consumption was reduced only in females at the top dose level by 10 to 20%. Measured body weight and feed consumption allowed exposure to be estimate as approximately 370, 770, and 1400 mg/kg/day.

During Task 2, 4 animals died: 2, 1, and 1 each in the low, middle, and high dose groups. During Task 2, the number of litters per pair decreased by 3% for the high dose group. No changes were noted

in the number of pups per litter, viability, or in adjusted pup weight. The slight reduction in number of litters per pair was judged to be too small to yield a detectable change during the statistically less powerful Task 3 crossover mating, so no crossover test was conducted.

For the  $F_1$  evaluation, the last litter in Task 2 from all dose groups was nursed to weaning and reared on the diet consumed by their parents.  $F_1$  pup body weights were reduced at all doses for both sexes by approximately 6 to 18%. Pup body weight gain to weaning was also reduced for the medium and high dose males (17 and 34%) and for females at all doses (10-28%).

All dose groups were reared consuming the same diet provided to their parents. The body weight differences that were seen during nursing were reduced, but still present, at the time of mating.

At the  $F_1$  mating, the  $F_2$  pup weight adjusted for litter size was decreased by 11% at the high dose level. No other reproductive end points were affected.

After the  $F_2$  pups were delivered and evaluated, the  $F_1$  adults from only the control and high dose groups were killed and necropsied. Compared to controls, the high dose males weighed 10% less, while organ weights were not affected. Sperm abnormalities increased from 7% (controls) to 16% at the high dose. High dose females weighed 8% less, while adjusted liver weight was increased by 10%.

In summary, the greatest toxicity produced by acetaminophen in the diet of Swiss mice was on the growing neonate. Fertility end points (ability to bear normal numbers of normal-weight young) were generally not affected.

# ACETAMINOPHEN

**Summary:** NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: 85204667/AS

Chemical: Acetaminophen

CAS#: 103-90-2

Mode of exposure: Feed

Species/strain: Swiss CD-1 mice

F <sub>0</sub> generation	Dose concentration →	0.25%	0.5%	1.0%
General toxicity		Male, female	Male, female	Male, female
Body weight		—, —	—, —	—, —
Kidney weight <sup>a</sup>		•	•	•
Liver weight <sup>a</sup>		•	•	•
Mortality		—, —	—, —	—, —
Feed consumption		—, —	—, —	—, ↓
Water consumption		•	•	•
Clinical signs		—, —	—, —	—, —

Reproductive toxicity			
̄ litter/pair	—	—	↓
# live pups/litter; pup wt./litter	—, —	—, —	—, —
Cumulative days to litter	—	—	—
Absolute testis, epididymis weight <sup>a</sup>	•	•	•
Sex accessory gland weight <sup>a</sup> (prostate, seminal vesicle)	•	•	•
Epidid. sperm parameters (#, motility, morphology)	•	•	•
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	•

F <sub>1</sub> generation	Dose concentration →	0.25%	0.5%	1.0%
General toxicity		Male, female	Male, female	Male, female
Pup growth to weaning		—, ↓	↓, ↓	↓, ↓
Mortality		—, —	—, —	—, —
Adult body weight		•	•	↓, ↓
Kidney weight <sup>a</sup>		•	•	•
Liver weight <sup>a</sup>		•	•	—, ↑
Feed consumption		—, —	—, —	—, —
Water consumption		•	•	•
Clinical signs		—, —	—, —	—, —

Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, ↓
Absolute testis, epididymis weight <sup>a</sup>	•	•	—, —
Sex accessory gland weight <sup>a</sup> (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	—, —, ↑
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Unclear
Study confounders:	None
NOAEL reproductive toxicity:	0.5%
NOAEL general toxicity:	<0.25%
F <sub>1</sub> more sensitive than F <sub>0</sub> ?	Yes
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. <sup>a</sup>Adjusted for body weight.